Centers for Education & Research on Therapeutics

a program of the Agency for Healthcare Research and Quality

July 1, 2004

Department of Health and Human Services

Re: Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Section 1013: Suggested Priority Topics for Research. Docket ID 2004S-0170.

The Centers for Education & Research on Therapeutics (CERTs) are pleased to submit recommendations for priority research topics pursuant to Section 1013 of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (MMA). While there are many important research topics, below are those the CERTs recommend to the HHS Steering Committee for the FY2006 priority list. Information gained through each of these research areas could be used to improve the appropriate use of prescription drugs and medical devices, and thereby the quality of care that patients receive under Medicare, Medicaid and the SCHIP programs.

1. Evaluation is needed regarding the knowledge about the safety and efficacy of 'off-label' use of marketed drugs in the form of evidence reports and systematic overviews where information is available. In current practice a high percentage prescription drug use occurs in situations that are not addressed in labeling. In addition most prescription medications used in children do not have adequate pediatric labeling. Consequently, the balance of risks and benefits in situations where drugs are used for indications not specifically addressed in labels has not been vetted through the rigorous evaluation process of the FDA. Relatively little research has been done about off-label use and the associated risks and benefits. Given the wide-scale off-label use of medical products, aggregated information about the value and direct analysis of gaps in knowledge should improve decision making to maximize the benefit of product use, while minimizing the risk. Approaches that could be used for analyzing and representing the evidence include the following:

- Convene expert meetings in major therapeutic areas (heart disease, psychiatry, rheumatology, etc) to identify the highest impact off-label uses of drugs.
- Prioritize literature searches based on highest impact uses of products.
- Produce annual reports of what is known, what is not known and recommendations for priority areas for clinical trials to clarify issues.
- Assess prescribing patterns (variation by geographic areas, provider specialty, frequency of inappropriate prescribing, and rates of adverse events) using available databases.

CERTs Coordinating Center
Duke Clinical Research Institute
P.O. Box 17969 • Durham, NC 27715
Fax: (919) 668-7166 • Phone: (919) 668-8543

2. Evidence report and systematic overviews need to be done to evaluate what is known about comparative effectiveness of drugs, and new evidence also needs to be developed regarding the comparative effectiveness of therapeutics. In most disease states at least one partially effective therapy is available, while in many high priority diseases such as HIV and heart disease, multiple therapies are in use at this time. Thus, the commonly asked question is not: 'Is this treatment effective?' Instead the question is: 'How does the balance of risks and benefits of this treatment compare with the balance of risks of benefits of another treatment?' In many cases, directly comparative clinical trials are not available, but even when they are, independent evaluation of the available data is frequently lacking. When directly comparative trials are not available, it is tempting to do either indirect comparisons from clinical trials or observational treatment comparisons, both of which are clouded by methodological issues. Better information about comparative effectiveness would significantly improve the prevention, treatment and cure of high priority diseases. In situations where more than one effective drug is available, information about patients who will benefit more from one particular drug will help patients, providers and policy-makers make decisions that will result in better health outcomes for patients. Approaches that could be used for analyzing and representing the evidence include the following:

- Convene expert meetings to define priorities for medical conditions and patient populations in which head-to-head comparisons are needed.
- Produce evidence reports and systematic overviews where data are available.
- Publish descriptive methodological papers on issues related to conducting comparative effectiveness studies.
- Conduct specific comparative analyses from existing databases where feasible and methodologically sound (e.g. identification/quantification of previously unrecognized adverse drug reactions; effects of patient factors on patterns of drug use, appropriateness, adverse events, adherence; effects of physician and system factors).
- Conduct direct comparison of commonly used regimens via practical clinical trials involving group-randomization of practices within health plans' defined populations.

3. Pharmacological and pharmacoepidemiological studies are needed to evaluate drug-drug interactions. The average Medicare patient takes 17 drugs per year. Because of the large number of drugs and because the interactions of many co-prescribed drugs are not adequately studied, many patients experience adverse reactions. This is especially true for many older drugs because information regarding their metabolism was not as extensively studied as part of the drug development process as it is today. There is even less evidence about the effect of alternative medications, such as herbal remedies, on the metabolism of drugs. If drug-drug interactions are better understood, drugs can be prescribed more safely. Approaches that could be used for analyzing and representing the evidence include the following:

- Convene “think tank” sessions to identify commonly associated medical conditions in the Medicare population and determine the greatest opportunities to improve patient safety through the study of potential drug-drug interactions that occur in the population.
- Use analytic capability of CERTs to quantify most common co-prescribed drugs in elderly patients from available databases.
- Conduct research to assess drug-drug interactions among the most commonly co-prescribed medications.

4. While the MMA provides for a new prescription drug benefit, medical devices will continue to play an important role in the evaluation and treatment of medical conditions. Because of different regulatory requirements, less information is often known about the benefits and risks (especially long-term) of medical devices than is known about drugs. In addition, medical devices can be very expensive. More complete knowledge is needed about the comparative effectiveness and off-label use of medical devices. Approaches that could be used for analyzing and representing the evidence include the following:

- Convene expert meetings in major therapeutic areas (heart disease, pediatrics, etc.) to identify the highest impact off-label uses of medical devices.
- Assess patterns of use (including off-label use) and associated outcomes using available databases. Examples of potential devices to study include the use of stents for cardiovascular disease and vertebroplasty/kyphoplasty for spinal compression fractures.
- Convene expert meetings to define priorities for medical conditions and patient populations in which head-to-head comparisons are needed.
- Examine the effects of prior authorization and other means of gatekeeping on device utilization.

5. Methodological studies are needed on the best approaches to Computerized Provider Order Entry (CPOE), including: classifying errors and flaws in CPOE systems, determining the most effective alerts built into CPOE systems to improve the balance of benefit and risk of CPOE, and assessing methods of combining CPOE data with clinical data to assess appropriateness of prescribing. The MMA mandates specifications for CPOE by 2008 and full implementation within one year after that. Despite the increasing implementation of CPOE systems, most of which are customized products, little research exists to create standards for this system. Early reports indicate that entirely new types of errors are being created from coding malfunctions and provider entry errors. No one is arguing that CPOE is not the appropriate concept, but the development of generalizable knowledge about CPOE is lagging behind the implementation of systems. In order to realize the potential of the system, research is needed to define best practices and clinically useful algorithms to improve prescribing. Approaches that could be used for analyzing and representing the evidence include the following:

- Develop consensus of CPOE error classification.
- Measure and quantify errors and subsequently conduct studies that evaluate approaches to minimize them.
- Assess the most common adverse drug interaction and dosing issues (e.g. inadequate dose adjustment for renal function) that could be addressed through CPOE.
- Test strategies to implement algorithms as alerts.
- Compare electronic merged datasets of clinical and CPOE data with case by case analysis of appropriateness of prescribing.
- Develop and test methods to increase clinicians' acceptance and effective use of CPOE, such as academic detailing which has been found to be effective in changing practice.

6. More studies are needed to understand and assess patient, clinician, and delivery system factors that influence appropriateness of prescribing, including both underuse and overuse, and test novel methods to improve appropriate prescribing. CPOE is an example of a delivery

system factor, but there are many others such as payment policies that affect prescribing and compliance with drug therapies. Preferred drugs lists are an example of a policy that may have unintended consequences that need to be better understood. Approaches that could be used for analyzing and representing the evidence include the following:

- Convene expert meetings to catalog what is known and unknown about delivery system factors (policy, technology, etc.) that influence appropriate prescribing behaviors.
- Identify and evaluate novel approaches to improve appropriate prescribing.
- Examine the benefits and risks of preferred drug lists.

We appreciate the opportunity to provide suggestions for research that can generate important information about how to improve the quality and safety of patient care.

Sincerely,

Robert M. Califf, M.D.
Principal Investigator, CERTs Coordinating Center